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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/173,463	10/14/1998	MARGARET E. BLACK	240052.429	1873

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EXAMINER	
FRONDA, CHRISTIAN L	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 04/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/173,463	BLACK, MARGARET E.	
	Examiner	Art Unit	
	Christian L. Fronda	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-60 is/are pending in the application.

4a) Of the above claim(s) 16-60 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-15 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-15 are under consideration in this Office Action.

2. The rejection of claims 2, 4, 5, and 7 under 35 U.S.C. 103(a) has been withdrawn. A new rejection under 35 U.S.C. 112, first paragraph, for these claims is stated below.

Claim Rejections - 35 U.S.C. § 112, 2nd Paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims refer to the mutations in the "Q substrate binding domain", 'DRH nucleoside binding site", and mutations at positions that are C- or N-terminal of these domains. However, the claims do not recite the specific amino acid sequence of the mutant *Herpesviridae* thymidine kinase. In view of this, one of skill in the art cannot determine the specific positions where these mutations occur. Amending the claims to recite the specific amino acid sequence and the specific positions of the mutations may overcome the rejection.

Claim Rejections - 35 U.S.C. § 112, 1st Paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with

the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-7 are genus claims that are directed toward any isolated nucleic acid molecule of any nucleotide sequence and structure encoding any *Herpesviridae* thymidine kinase enzyme having any at least one mutation in the Q substrate binding domain where said mutation increases any biological activity of said thymidine kinase. Claims 8-15 are genus claims that are directed toward any isolated nucleic acid molecule of any nucleotide sequence and structure encoding any *Herpesviridae* thymidine kinase enzyme having any at least one mutation in the Q substrate binding domain where said mutation results in a thymidine kinase that is capable of phosphorylating any nucleoside analogue including the analogues recited in claim 11.

The scope of the claims includes many nucleic acid molecules with widely differing structural, chemical, and physical characteristics and many mutations that result in any increase of any biological activity of the encoded thymidine kinase or results in the encoded thymidine kinase that is capable of phosphorylating any nucleoside analogue. Furthermore, the genus is highly variable because a significant number of structural differences between genus members exists.

The specification provides general guidance for randomly mutating a polynucleotide of SEQ ID NO: 1 to create mutant polynucloetides having non-wild-type nucleotides for codons corresponding to amino acid residues 112-132 (Q substrate binding domain) of the encoded Herpesviridae thymidine kinase (see Example 10, pp.87-88). The specification states that mutants were assayed for ability to phosphorylate thymidine, acyclovir, and ganciclovir (see p. 88, lines 19-24).

However, the specification does not provide a written description of a specific nucleotide sequence encoding a specific amino acid sequence of mutant *Herpesviridae* thymidine kinases that have mutations in Q substrate binding domain where such mutations result in a thymidine kinase that has any increase of any biological activity or ability to phosphorylate any nucleoside analogue. The specification fails to define those structural features that are commonly possessed by members of the claimed genus that distinguish them from other *Herpesviridae* thymidine kinases. Thus, one skilled in the art cannot visualize or recognize the identity of the members of the claimed genus.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definitions, such as the structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v, Eli Lilly and Co.* 43 USPQ2d 1398 (Fed. Cir. 1997), quoting *Fiers v. Revel,* 984 F.2d 1164, 1171, 25 USPQ2d

1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe the genus of genetic materials, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics for the claimed molecules, e.g. structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In view of the above considerations, one of skill in the art would not recognize that applicants were in possession of the necessary common features or attributes possessed by members of the claimed genus of isolated nucleic acid molecules of any nucleotide sequence and structure encoding any *Herpesviridae* thymidine kinase enzyme having any at least one mutation in the Q substrate binding domain where said mutation increases any biological activity of said thymidine kinase, and the claimed genus of isolated nucleic acid molecules of any nucleotide sequence and structure encoding any *Herpesviridae* thymidine kinase enzyme having any at least one mutation in the Q substrate binding domain where said mutation results in a thymidine kinase that is capable of phosphorylating any nucleoside analogue.

Furthermore, claims 1-7 fails to comply with the written description requirement for the following additional reasons. Claims 1-7 encompass any "increase in biological activity" where such activity includes thermal stability, enzymatic activity, resistance to inhibitors. However, the specification only describes in general terms that mutant *Herpesviridae* thymidine kinase were assayed for ability to phosphorylate thymidine, acyclovir, and ganciclovir (see p. 88, lines 19-24). Thus, one of skill in the art would not recognize that applicants were in possession of polynucleotides encoding any mutant *Herpesviridae* thymidine kinase enzyme having any at least one mutation in the Q substrate binding domain where said mutation increases any "biological activity".

7. Claims 2, 4, 5, 7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized In re Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or

unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of claim 2 encompasses any isolated nucleic acid molecule encoding any mutant *Herpesviridae* thymidine kinase having at least three mutations which increases any biological activity; claim 4 encompasses the said isolated nucleic acid molecule further comprising at least one amino acid substitution located 4, 5, 6 amino acid toward the C-terminus from a DRH nucleoside binding site; claim 5 encompasses the said isolated nucleic acid molecule further comprising at least one amino acid substitution located from 1-7 amino acid toward the N-terminus from the DRH nucleoside binding site; and claim 7 encompasses the said isolated nucleic acid molecule where the said enzyme is truncated or contains an in-frame deletion.

The specification provides general guidance for making for randomly mutating a polynucleotide of SEQ ID NO: 1 to create mutant polynucloetides having non-wild-type nucleotides for codons corresponding to amino acid residues 112-132 (Q substrate binding domain) of the encoded *Herpesviridae* thymidine kinase (see Example 10, pp.87-88). However, the specification does not provide specific guidance or prediction regarding how to make the claimed polynucleotides without undue experimentation.

The amount of experimentation to make the claimed polynucleotide is enormous and undue because such experimentation is trial and error experimentation to search and screen for the claimed polynucleotides. Such experimentation entails making specific nucleotide(s) change(s) (deletion, insertion, substitution, or combinations thereof) in a polynucleotide and screening, searching, and assaying for any polynucleotide that encodes the claimed polynucleotides encoding the mutant thymidine kinase enzymes (full-length or truncated) with the claimed any increase in any "biological activity". General teachings regarding screening or searching for the invention is not guidance for making the claimed invention.

Thus, such experimentation is well outside the realm of routine experimentation, and without guidance or prediction, the amount of experimentation left to those skilled in the art for making the claimed polynucleotides is undue.

Claim Rejections - 35 U.S.C. § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in

> section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1, 3, 6, 8-11 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Munir et al. in view of Graham et al., Kit et al., Drake et al., Waldman et al., Munch-Petersen et al., Balasubramaniam et al., Brown et al., and Donarian et al. The teachings of each of the references have been stated in the previous Office Action.

Applicant's arguments filed November 29, 2000, have been fully considered but they are not persuasive. Applicant argues that the claims are neither taught nor suggested by the teachings of Munir or any of the secondary references in combination with the teachings of Munir.

As stated in the previous Office Action, Balasubramaniam et al. and Brown et al. teach that the Q substrate binding domain and the DRH binding domain are important in nucleoside binding and that in order to obtain mutants having the desired properties (i.e. increased enzyme activity or greater substrate/analog/prodrug specificity) this region must be modified. One of ordinary skill in the art would have used the random mutagenesis method taught by Munir et al. to randomly mutate the codons encoding these important domains in order to obtain and screen for mutants with enhanced properties such as greater substrate, analog, or prodrug specificity and that such mutants having increased activity toward prodrugs such as ganciclovir are expected to be more effective in the treatment of cancer when these mutants are used in gene therapy as taught by Donarian et al. Accordingly, claims 1, 3, 6, 8-11 stand rejected.

10. Claims 12-15 stand again rejected under 35 U.S.C. 103(a) as being unpatentable over Esandi et al. in view of Munir et al., Graham et al., Kit et al., and Donarian et al. The teachings of each of the references have been stated in the previous Office Action.

Applicant's arguments filed November 29, 2000, have been fully considered but they are not persuasive. Applicant argues that claims 12-15 are neither taught nor suggested by the teachings of Esandi et al. or any of the secondary references in combination with the teachings of Esandi et al.

As stated in the previous Office Action, Esandi et al. teach a vector containing the cytomegalovirus immediate early promoter and the herpes simplex thymidine kinase gene; gene therapy of experimental malignant mesothelioma using this vector; and potential use of this gene therapy as a local treatment for malignant mesothelioma; and Donarian et al. further teach that the α fetoprotein promoter (a tissue specific promoter) is suitable in the control of prodrug activating or toxic enzymes in the gene therapy of cancer.

As stated in the previous Office Action, it would have been obvious to one of ordinary

skill in the art at the time the invention was made to make an expression vector comprising a promoter operably linked to the claimed nucleic acid encoding the claimed *Herpesviridae* thymidine kinase by inserting the mutated DNA encoding mutant thymidine kinase described above in the rejection of claims 1, 3, 6, 8-11 into the expression vector taught by Esandi et al. in order to express thymidine kinase mutants in cancer cells of specific tissue origin which is expected to be effective in the treatment of cancer when these mutants are used in gene therapy as taught by Donarian et al.

Conclusion

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christian L Fronda whose telephone number is (571)272-0929. The examiner can normally be reached Monday-Friday between 9:00AM - 5:00PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura N Achutamurthy can be reached on (571)272-0928. The fax phone number for the organization where this application or proceeding is assigned is (571)273-8300.

13. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CLF